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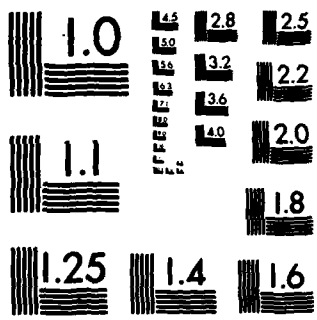

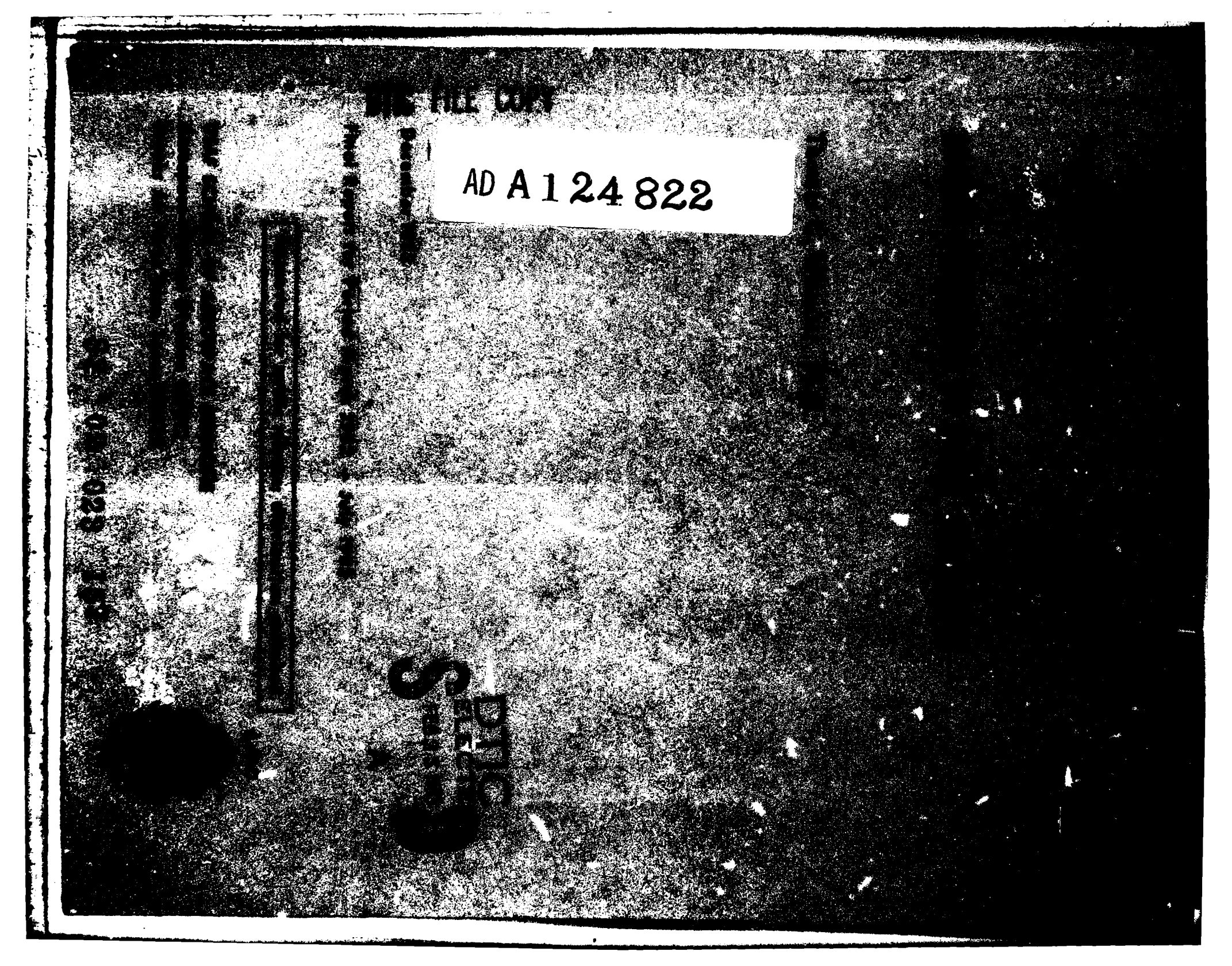

The research involved in this study was reviewed, approved, and monitored in accordance with the Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council.

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

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A low-level exposure to an electron beam has been shown to produce amnesia. Arguments are presented which suggest one mode of CNS activation may have been via visual stimulation. This hypothesis was tested by determining if a photoflash could also produce amnesia using the same task (single trial avoidance). The author shows that a photoflash is an adequate stimulus in amnesia production, and that the extent of amnesia is intensity dependent. Therefore, one possible mechanism of CNS activation by an electron beam may be via visual stimulation.

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20. ABSTRACT (continued)
Unknown remain the extent to which other sensory systems may be activated, and the effects of such activation on other CNS functions.

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Illustrations

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AMNESIA PRODUCTION BY VISUAL STIMULATION

INTRODUCTION

Low-level (8 rad at 10^8 rad/sec) exposure to an electron beam has recently been shown to produce amnesia in mice (10). This result is totally unexpected. No form of ionizing radiation has previously been reported to produce a performance deficit at such low exposure levels. Bruner and coworkers (3), for example, demonstrated a memory decrement using cobalt-60 irradiation, and reported the threshold for the effect to be 300 rad. This dose was some 40 times larger than that used by McNulty and Pease (10), who demonstrated a memory deficit at 8 rad.

Amnesia is a central nervous system (CNS) function and, therefore, the electron beam must have modified neural activity in the CNS. Two mechanisms for CNS activation are known: (a) energy deposit in the CNS sufficient to activate neurons directly; or (b) providing a CNS input via one or more of the sensory systems. A review of the literature strongly suggests that direct CNS activation could not have produced amnesia at such low electron beam exposure levels. Direct activation of neurons in the CNS by various forms of ionizing radiation requires very large exposure levels (<1000 rads--consult Ref. 9 for review).

As compared with the high dose levels required to activate CNS neurons directly, only minute dose levels are needed to stimulate the CNS via some of the sensory systems. The visual system has been shown to be among the most sensitive to ionizing radiation. Visual thresholds have been reported to be only 0.5 mrad (x-ray) for human subjects (8,11). Smith and Kimeldorf (12) determined electroretinogram thresholds for the moth to be as low as 0.25 mrad for electron exposure. High energy electrons would be much more efficient in stimulating the visual system than would other forms of ionizing radiation. Electrons with energies above 1 MeV transfer energy by emitting electromagnetic energy in the form of visual light, in addition to ionization (Appendix A: Part 1). Therefore, an 8-rad exposure (such as that used by McNulty and Pease (10)) may be equivalent to presenting a short flash of light about 10^6 above absolute visual threshold. If the hypothesis is that electron beam exposure modified CNS activity via sensory stimulation, then a visual stimulus of similar duration and intensity should also produce amnesia under the same experimental conditions.

METHODS

The task was a single trial avoidance paradigm. The procedure was to place the animal in a small aversive chamber with a background light-level of 50 $\mu W/cm^2$. After a 10-sec adaptation period, a door opened and provided access to a large dark ("preferred") chamber. The time required for the animal to leave the illuminated ("aversive") chamber and enter the preferred chamber

was the measure of interest (denoted "T"). Once the animal was inside the preferred chamber, a footshock of 85 V peak-to-peak (P-P) was delivered for 1 sec (BRS Instruments, Model No. SGS-001). (The method of selecting the shock level is discussed in Appendix A: Part 2.) One second after the termination of the shock, a photoflash was presented. The animal was then returned to its home cage. A second trial on the same task was run after a fixed time period. The second trial consisted of placing the animal in the aversive chamber and monitoring the time (T') required for the animal to enter the preferred chamber. No shock or flash was presented on the second trial. A maximum of 100 sec was allowed for the animal to enter the preferred chamber on the second trial. (The apparatus is described in detail in Appendix A: Part 3.)

The operational definition of the extent of amnesia production was the mean value of T' - T across the test group. If the animal recalled the shock treatment on the first trial, the value of T' - T would be large. If the photoflash interfered with the animal's ability to recall the shock, then T' - T would be greatly reduced.

To simulate the short pulse duration of an electron beam exposure (10^{-5} - 10^{-8} sec), a photoflash unit was used (10×10^{-6} sec flash-Grass Photo Stimulator PS 22C). The flashbulb mount was positioned against the outside clear wall of the preferred dark chamber, approximately 5 cm from the animal. The highest intensity used (I = 16) was 19×10^{6} Lu (peak), as specified by the manufacturer. This intensity could be reduced by a factor of 16 in binary steps.

One hundred and fifty Sprague-Dawley rats (male, 240 g + 20 g) were purchased from Hill Top Inc. All animals were individually housed under a 12-hr-ON, 12-hr-OFF light cycle with free access to food and water. The experiments were run from 0900 to 1400 hr in the spring. Animals were randomly selected for the experimental groups listed in Table 1:

TABLE 1. EXPERIMENTAL GROUPS AND TEST CONDITIONS

Group No.	Experimental conditions	Time to second trial (hr)
1	Shock plus flash (I = 16)	1
2	No shock plus flash (I = 16)	1
3	Shock plus no flash	1
4	No shock plus no flash	1
5	Shock plus flash (I = 8)	1
6	Shock plus flash (I = 4)	1
7	Shock plus flash (I = 2)	1
8	Shock plus flash (I = 16)	4
9	Shock plus no flash	4
10	Shock plus flash (I = 16)	24
11	Shock plus no flash	24
12	Preexposure to photoflash then shock plus flash (I = 16)	1

Eleven animals were assigned to each of the 12 groups. Groups 10 and 11 were included to duplicate the test trial interval employed in the McNulty and Pease study (10). Group 12 was included to determine if preexposure to the photoflash would alter its effectiveness in amnesia production. Animals in this group were given a "No shock plus flash" trial, 1 hr before the normal treatment trial. The test groups were run on three test days--Day 1: Groups 1, 2, 3, 4; Day 2: Groups 5, 6, 7, 8; and Day 3: Groups 9, 10, 11, 12. On each test day, animals were tested sequentially across groups; i.e., one animal from Group 1, and then one from Groups 2, 3, 4, 1, 2, etc., until all eleven animals from each group had been run.

RESULTS

The results are presented in Table 2 and Figure 1, with second trial latency (T') minus first trial latency (T) being the dependent variable (in seconds).

TABLE 2. EXPERIMENTAL RESULTS--LATENCY SCORES (T' - T) IN TERMS OF MEAN, STANDARD DEVIATION (SD), AND STANDARD ERROR OF THE MEAN (SEM) ACROSS TEST CONDITIONS

Time to second trial	T'-T	Shock plus no flash	Shock plus flash (I=16)	No shock no flash	No shock plus flash (I=16)
		Group 3	Group 1	Group 4	Group 2
1-hr	Mean	24.8	1.8	-2.7	-1.6
	SD	25.19	4.5	5.5	3.3
	SEM	8.0	1.4	1.7	1.1
		Group 9	Group 8	- - - - - - - - - - - - - - - -	
4-hr	Mean	24.2	3.1	Preexposure to	
	SD	33.2	5.9	photoflash then shock	
	SEM	10.5	1.9	plus flash (I=16)	
		Group 11	Group 10	Group 12	
24-hr	Mean	18.5	2.0	37.0	
	SD	22.9	5.6	39.6	
	SEM	6.6	1.6	12.4	

In summary, the data in Table 2 and Figure 1 clearly indicate the following: (a) The photoflash alone was not an aversive stimulus (compare Groups 2 and 4). (b) The animals clearly recalled the aversive shock when it was not followed by a flash (considerable hesitation to enter the preferred chamber on the second trial: Groups 3, 9, and 11). (c) A photoflash just after the termination of the shock greatly reduced the recall of the aversive shock (compare Groups 3 and 1, or 9 and 8, or 11 and 10; ($P<.05$ in all cases). (d) The extent of amnesia is related to the intensity of the photoflash (Fig. 1). (e) Exposing animals to the test conditions (chamber and photoflash), prior to performing the task, eliminated the effectiveness of the photoflash in producing amnesia (compare Groups 1 and 12, $P<.05$). These conclusions are based on observations of the animals and supported by the analytical data.

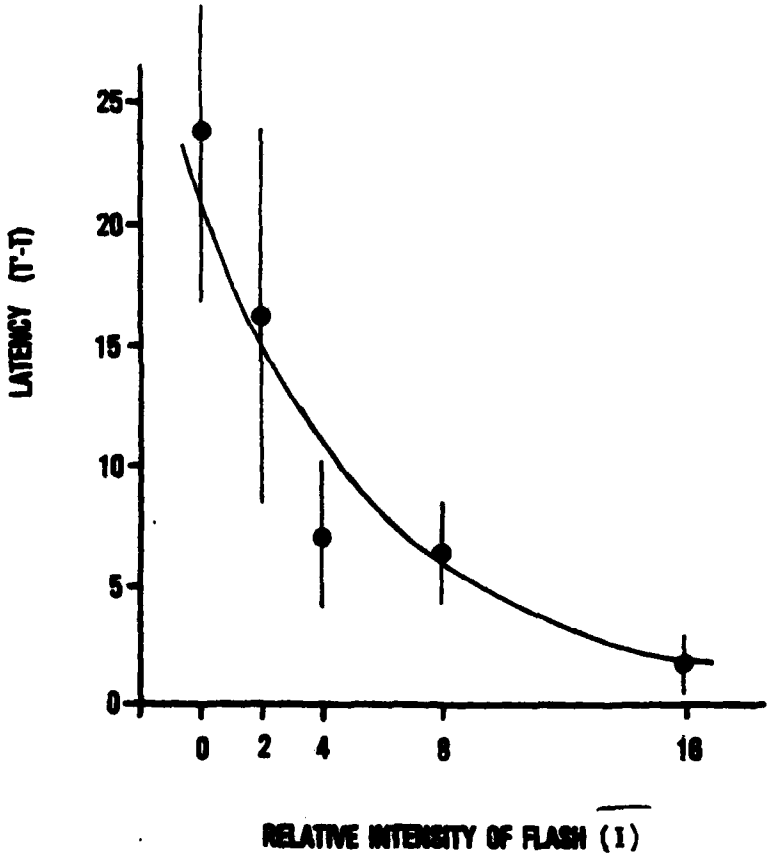

Figure 1. The latency (mean ± SEM) to enter the preferred chamber (trial 2 - trial 1; T' - T) in seconds vs. the intensity of the photoflash (I). These data can be modelled by an exponential function: $T' - T = 20.5e^{-0.16\ I}$, with a coefficient of determination, $r^2 = 0.95$, and are from groups 1, 3, 5, 6, and 7.

Complete statistical analyses of these data are presented in Appendix A: Part 4. Observational data: The analytical data represent only a part of the animal's response. For example, animals which received no shock (with or without flash: Groups 2 and 4) were easy to handle on the second trial. Once placed in the aversive chamber, they approached the door and entered immediately upon the door opening, thus reacting faster than in the first trial. Those animals which had received shock alone were aggressive and under apparent stress. Upon observation, the difference between the treatment groups was obvious, and is reflected in the latency data.

DISCUSSION

These data clearly demonstrate that a photoflash is an adequate stimulus to produce amnesia in rats. This finding does not suggest that the visual system is the only sensory system which can produce amnesia. Any other sensory system might also provide sufficient input to the CNS to mask the input due to the aversive shock; i.e., produce amnesia. In other terms, the "recency theory" (2) appears to apply here. [The recency theory states that, if a series of novel stimuli are presented, the subject will most vividly recall the stimulus presented last (most recently) (2).] This study employed two novel stimuli: one aversive (shock), and the other not aversive (photoflash). Clearly these data support the recency theory, since the aversive stimulus was not recalled. The theory is also supported by the preexposure data (Group 12). Preexposing the animal to the photoflash eliminated the novelty of this stimulus, and the animal recalled the last novel stimulus presented: the shock.

A method by which an electron beam exposure could produce a photoflash within the eye has been discussed (Appendix A: Part 1). However, ionizing radiation is known to stimulate all sensory systems, with various degrees of efficiency (6,8,9). An electron beam exposure would produce activity in all sensory systems simultaneously and, therefore, provide a much greater extent of CNS activation than visual stimulation alone. Any stimulus which simultaneously activated the auditory, visual, olfactory, etc., systems would indeed be a novel stimulus. An interesting subject for future research would be to ascertain the effectiveness of an electron beam in producing amnesia across a large dose and dose-rate range, and to compare these data to those produced using conventional sensory stimuli. Also, preexposure to an electron beam pulse may eliminate its effectiveness in producing amnesia. That is, electron beam preexposure may possibly reduce the novelty aspects of the stimulus (1, 4, 5).

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APPENDIX A

Part 1. Efficiency of Particle Beam Exposure In Visual Stimulation

In addition to stimulating photoreceptors via ionization, energetic particles also produce electromagnetic energy (quanta) in the visible range: i.e., when the velocity of a particle is greater than the velocity of light in the same media, energy is emitted in the form of electromagnetic energy (EME) (Cerenkov radiation; (7)). The emitted EME has a continuous spectrum covering the visual range. Approximately 200 quanta/cm are emitted from 400 to 700 nm for a single electron with an energy greater than 1 MeV. The mean energy of the electron beam used in the McNulty and Pease study (10) was greater than 10 MeV. I have calculated that an exposure of 8 rads (2×10^7 quanta/cm/ rad) would produce over 3.2×10^8 absorbable quanta within the eye. This calculation takes into account the ocular path length and spectral sensitivity function. Finally, in addition to stimulating the visual system via ionization, an electron beam exposure also produces absorbable visual light. Therefore, particle beam exposure would be many times more efficient in stimulating the visual system than other forms of ionizing radiation.

Part 2. Selection of Shock Parameters

A pilot study employing 82 rats was performed, using shock only, and T' as a function of shock level was determined. For shock levels of less than 40 V, the T' distribution was concentrated at the lower limit, being between 0 and 2 sec. As the shock level was increased, the distribution became normal with a mean between 15 and 45 sec. At higher shock levels (above 100 V) the distribution became bimodal, with some animals reluctantly entering the preferred chamber in less than 50 sec--and with others refusing to enter (T' greater than 300 sec). Increasing shock levels simply increased the number of animals that refused to enter the chamber, and shifted the distribution to the upper limit. The shock level selected for this study was midway between the points where shock became aversive (T' greater than T), and the distribution became bimodal. Therefore, the treatment (photoflash) could increase or decrease the mean T' while the distribution remained normal.

Part 3. Apparatus for Evaluating Memory Deficits in Rats

This report section describes the physical apparatus used to evaluate experimentally induced memory deficits. The procedures and apparatus were designed in a general format for use in determining the effects of drugs,

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EDITOR'S NOTE: The references cited in Appendix A are drawn from the author's list on pp. 7 - 8.

ionizing radiation, directed energy, etc., in producing memory deficits. The device described here has an automated event-timing circuit, in order to reduce trial-to-trial variance, and remote control which removes the experimenter from the environment.

The control unit is a simple timing and recording device (Figs. A-1 and A-2) which controls the sequence of events. The test sequence is initiated by depressing the reset switch (S1), thus insuring that all counting and timing circuits are clear. Depressing S2 starts the T_1 counters and provides a preset delay between the time S2 is depressed and the door opens. This time delay (T_1) can be set to any desired interval between 1 and 16 sec (Fig. A-2). At the end of the preset interval, the door is opened via a relay driver (A19). Once the animal has entered the preferred chamber, S3 is depressed. Depressing S3 closes the door, turns on the shocker, and starts the T_3 timing circuit. The T_3 timing circuit provides a fixed time delay between the inactivation of the shock and the start of the treatment. As shown in Fig. A-2, T_3 may be preset between 0.1 and 1.6 sec. At the end of T_3, a switch closure (via A20) is provided to control any treatment control device. The data (T_2) can then be read off the indicator cards (A11-A13) or printed out via the counter-printer by resetting the system (depressing S1). A detailed description of the equipment, component interconnections, and specifications is provided by Figures A-1 and A-2.

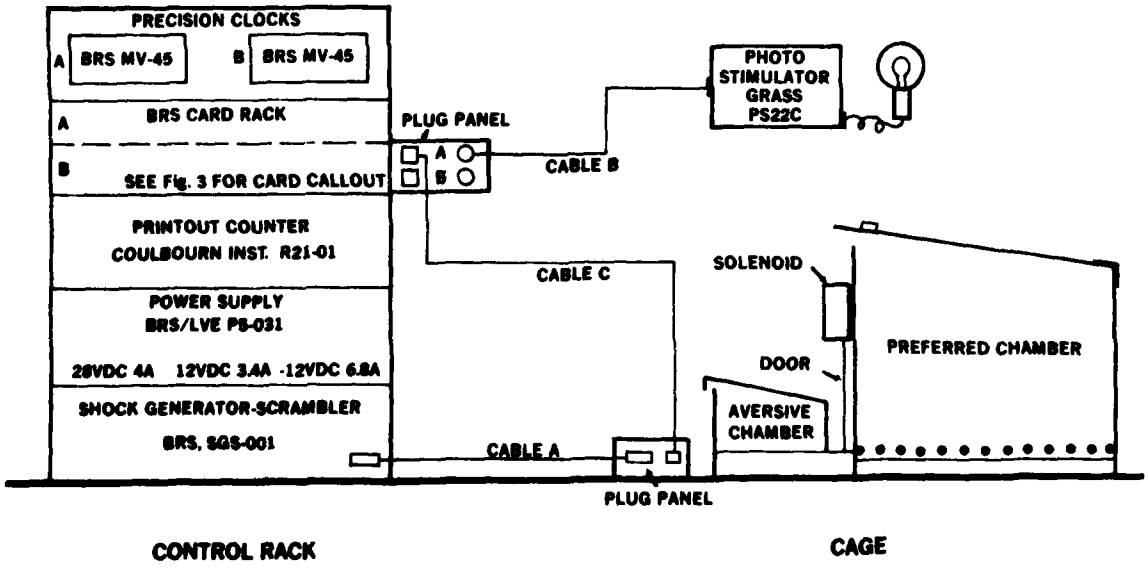


Figure A-1. Behavioral apparatus schematic diagram. [Within this diagram, Fig. 3 = Fig. A-2; View b]

(Fig. A-1 legend continued on facing page)

(Fig. A-1 legend continued from facing page)

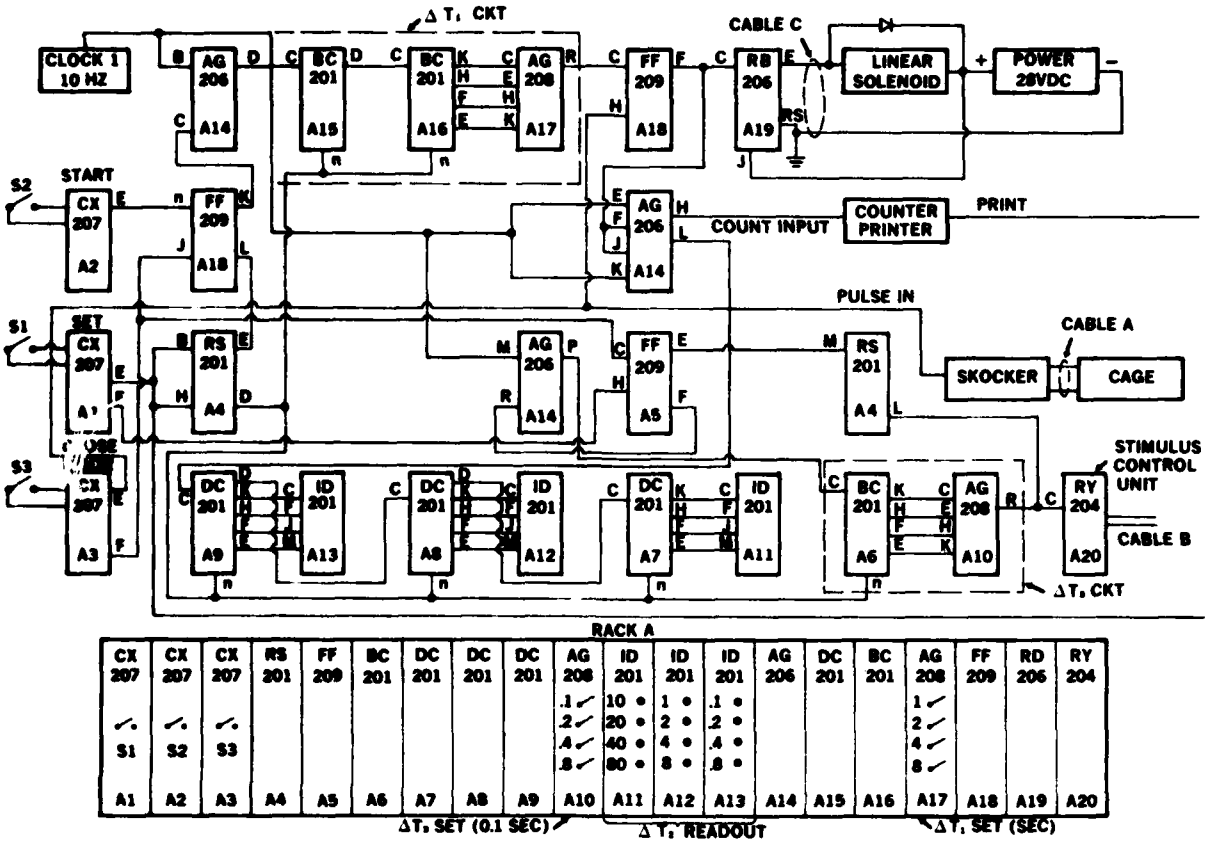
The control rack contains the components for timing control, T_2 read and/or printout, shock control, and system power. The wiring diagram for interconnection of these components is illustrated in Figure A-2. The BRS Instruments card rack contains two duplicate systems (denoted "A" and "B"). This duplication increases reliability and decreases downtime during field operation. The control rack is connected to the external components via three 80-ft cables (Fig. A-2: View b). The long cables permit use in locations where the operator cannot be in the vicinity of the cage (radiation exposure rooms, etc).

Cable B is connected to a relay (RY204 in position A20) which is closed at the end of T_3 in order to control or signal the start of the treatment. Here, the switch closure served as a trigger to the photo stimulator.

Cables A and C connect the control rack to the cage. Cable A provides the grid shock lines from the shock generator. These shock lines are hard-wired from the cage plug panel to the individual shock bars which make up the floor in the preferred side of the cage (see Fig. A-2: View b, for wiring).

Cable C provides power to drive the solenoid to open and close the door between the two chambers of the cage (Fig. A-2: View b).

The cage consists of two chambers separated by a 6.3 x 6.3 cm doorway. The aversive chamber is 5.7 x 5.7 x 16.5 cm, with a door on the top, as shown. The preferred chamber is 21.6 x 27.9 x 20.3 cm, with black walls and ceiling and a shock grid floor; the top of the chamber opens for easy removal of animals.

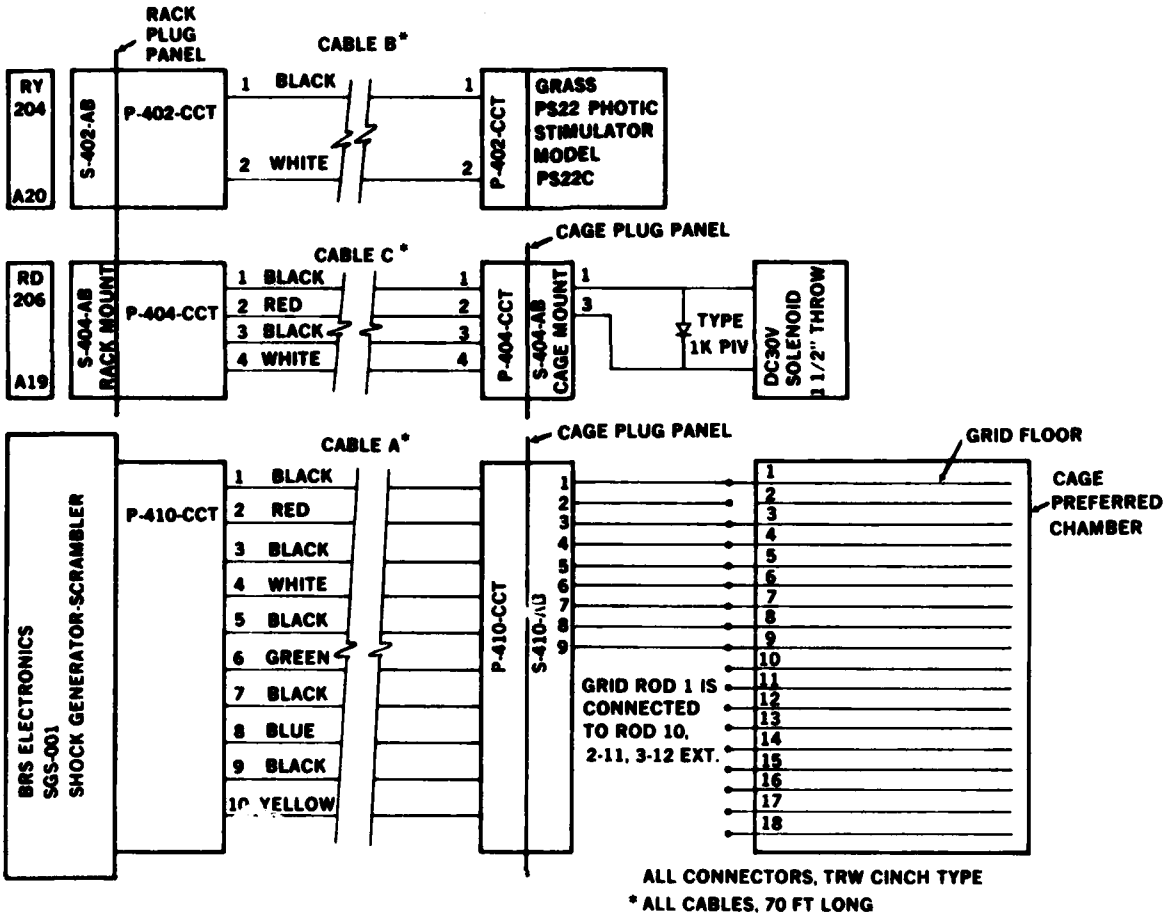


(View a)

Figure A-2: Views a and b. Behavioral apparatus wiring diagram.

The control components of the system are BRS timers and logic cards. Cards are denoted by the small boxes. Each box (BRS card) is labeled as to card type and location in the card rack. Fig. A-2, View b, illustrates each card's position in the rack. Card position A10 contains an AG208 (selectable input AND gate). The numbers to the left of each switch are delay time in seconds. The delay times for setting T_3 are additive; i.e., if switch 1 and 3 (from the top) are in the up position and switches 2 and 4 are in the down (off) position, the delay time for T_3 will be 0.1 + 0.4 sec. The same scheme is true for setting the T_1 delay using the AND gate in position A17. The range of selectable delay times for T_1 are 1-16 sec and for T_3 are 0.1-1.6 sec.

(Figure legend continued on facing page, under "View b")



(View b)

Figure A-2. (Figure legend continued from facing page)

The ID 201 cards in positions A11-A13 provide a readout of T_2. The black dots represent indicator lamps and the numbers to the left of each are in seconds. When S3 is depressed (close door) the T_2 counter is stopped and the ID 201s display the T_2 value in gray code until the system is reset via S1. When S1 is depressed, the information (T_2) is also automatically printed out via the counterprinter.

Part 4. Data Analyses

Three analyses of variance (ANOVAs) were calculated. The first analysis was a 2 X 2 for Groups 1-4 (Table A-1).

TABLE A-1. COMPARISON OF PHOTOFLASH AND SHOCK

		Shock	
		Yes	No
Flash	Yes	1[a]	2
	No	3	4

[a]Group number

Significant differences were present between the shock, no shock conditions (P = 0.0004) and between the flash, no flash conditions (P = 0.0088). A significant interaction was also present between shock and flash (P = 0.0043).

The second ANOVA was calculated on Groups 1, 3, 8, 9, 10, and 11 as a function of time to second trial. This ANOVA was a 3 X 2 (Table A-2).

TABLE A-2. COMPARISONS ACROSS DELAYS TO SECOND TRIAL

Time to second trial	Shock plus flash	Shock no flash
1 hr	1[a]	3
4 hr	8	9
24 hr	10	11

[a]Group number

A significant difference existed between those flash and/or no flash conditions (P = 0.0001) with no difference among times (P = 0.8343) and no interaction between flash and time (P = 0.9095).

The third ANOVA was a 1 X 5 on the intensity of flash data (Table A-3 and Fig. A-1).

TABLE A-3. COMPARISONS ACROSS FLASH INTENSITIES

Intensity of flash	Group No.
I = 0	3
I = 2	7
I = 4	6
I = 8	5
I = 16	1

The probabilities of differences between the intensity groups (P-values) are tested, as follows:

	I = 0	I = 2	I = 4	I = 8	I = 16
I = 0	1.000				
I = 2	0.253	1.000			
I = 4	0.021	0.229	1.000		
I = 8	0.016	0.189	0.911	1.000	
I = 16	0.003	0.057	0.468	0.538	1.000